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5 pages total
From: T. Kowalski

PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Walker et al.
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For	:	REGULATION OF INTRACELLULAR GLUCOCORTICOID CONCENTRATION
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DECLARATION AND SUPPLEMENTAL RESPONSE TO OFFICE ACTION AND TO MATTERS DISCUSSED DURING INTERVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Dear Sir:

PROFESSOR BRIAN WALKER DECLARES AND SAYS THAT:

1. Attached to the confirmation copy of this paper, that I understand is being filed by Express Mail, is a true copy of the Powerpoint presentation that I presented with Professor Jonathan Seckl, Drs. A. Maschio and C. Soames, and Thomas J. Kowalski, Esq., to the Examiner Kantamneni and SPE Padmanabhan, both of whom are thanked for the courtesies extended during the personal interview on 1 March 2006.

2. During the interview there was a question as to text in Walker et al. that reads:

> We suggest that in man carbenoxolone inhibits both 11 β-dehydrogenase and 11 β-reductase activities. Measurement of plasma cortisol and cortisone in samples obtained by selective venous catheterization demonstrates that the equilibrium between 11 β-dehydrogenase and 11 β-reductase activities varies between organs, such that 11 β-dehydrogenase is predominant in the kidney and 11 β-reductase is predominant in the liver. Thus simultaneous inhibition of both activities could result in increased intra-renal cortisol concentration but decreased intra-hepatic cortisol concentration ...

3. The cited prior art (Walker et al.) states that carbenoxolone inhibits both 11β-reductase and 11 β-dehydrogenase activities. It indicates that the 11 β-reductase is predominant in liver and the 11 β-dehydrogenase is predominant in kidney, so that inhibition by carbenoxolone would increase cortisol levels in kidney and decrease cortisol levels in liver.

4. As discussed in the interview, inhibition of both 11 β-reductase and 11 β-dehydrogenase activities is a property of many inhibitors of 11 β-HSD1 which were known in the art at the priority date (see Monder and White, Vitamins and Hormones 1993).

5. Practice of the claimed invention does not require an inhibitor which is selective for either reductase or dehydrogenase activity. Rather, the effect of any inhibitor of the enzyme in a tissue depends on the predominant reaction direction of the enzyme in that tissue. In a tissue with predominant dehydrogenase activity, e.g., vascular smooth muscle as discussed during the interview, any inhibitor will increase local cortisol levels. In a tissue with predominant reductase activity, such as adipose tissue or neuronal tissue (CNS), any inhibitor will decrease local cortisol levels.

6. The present invention is specific to the predominant reaction direction of 11 β-HSD1 (reductase) in adipose tissue or neuronal tissue (CNS). The present invention provides the use of inhibitors of 11 β-HSD1 in patients in need of lower glucocorticoid levels in adipose

tissue and CNS tissue, e.g., patients with obesity, insulin resistance, elevated fatty acids, cognitive dysfunction. There is no teaching or suggestion in Walker et al to select adipose tissue or CNS tissue as targets for 11 β-HSD1 inhibition. Moreover, there is no indication or suggestion as to the action of carbenoxolone to either increase or decrease cortisol concentrations within adipose tissue or CNS tissue. There is nothing in Walker et al., and more generally the in prior art, that teaches or suggests that inhibition of 11 β-HSD1 in adipose or neuronal tissue results in inhibition of reductase activity and lowering of cortisol concentration in those tissues. There is no motivation in Walker et al. to select adipose tissue or neuronal tissue from the numerous types of tissues found in man.

7. As described in the presentation during the interview, there are numerous ways in which 11 β-HSD1 can function in any given tissue: it may function as a predominant dehydrogenase, it may function as a predominant reductase, it may function with bidirectional activity, or it may function with no activity, e.g., due to being not present or not active. The skilled artisan reading the cited prior art (Walker et al.) would need to know the predominant reaction direction in adipose and CNS in order to predict whether carbenoxolone or any other inhibitor would increase, have no net effect, or decrease cortisol concentration in adipose tissue and neuronal tissue (CNS). It is only by virtue of the teachings in the present application that the skilled person is provided with the knowledge that 11 β-HSD1 functions as a reductase in adipose and CNS tissue, and is taught that inhibition of 11 β-HSD1 in adipose tissue and CNS tissue lowers cortisol concentrations in these tissues (and can thereby provide for lowering glucocorticoid levels in adipose tissue and CNS tissue of patients with obesity, insulin resistance, elevated fatty acids, cognitive dysfunction).

8. Indeed, as described in the presentation during the interview, the prior art specifically taught that 11 β-HSD1 was a predominant dehydrogenase in adipose tissue and CNS tissue. Moreover, the prior art taught that inhibitors of 11 β-HSD1, including carbenoxolone, would increase cortisol action by inhibiting 11 β-dehydrogenase in CNS tissue. In short, the prior art taught away from the instant invention. Thus, reading Walker et al., the skilled person would deduce that carbenoxolone would do the same in adipose tissue and CNS tissue as it does in kidney, that is, inhibit a dehydrogenase and thereby increase cortisol concentrations. Reading Walker et al. and the prior art in its entirety, the skilled artisan would not be motivated to inhibit

11 β-HSD1 in adipose tissue and CNS tissue because the skilled person would not expect that this would lower cortisol levels in these tissues.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated: March 1st 2006 By: _____
Professor Brian Walker